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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/346,910	11/30/94	LIPTON	S 00108017004

EXAMINER

~~HM21/0428~~

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ART UNIT	PAPER NUMBER
1645	16

DATE MAILED: ~~04/28/98~~

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/29/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 2-10 is/are pending in the application.
Of the above, claim(s) 2-7 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 8-10 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☑ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

3. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record and the following.

The specification contains reference to a deposit known as ATCC 75949. It does not refer to a deposit known as ATCC 97525, as recited in the instant claims. This is a new matter rejection.

Applicant's arguments filed 11/19/98 have been fully considered but they are not persuasive because Applicant argues that deposit 97525 is a deposit of clone TR2B packaged in a lambda gt11 phage (Paper No. 19, page 2, filed 11/19/98). However, the specification on page 8, lines 30-31, indicates that clones TR2A and TR2B have accession number 75949. The specification does not recite clone TR2B packaged in a lambda gt11 phage, and therefore, the new matter rejection is maintained for the simple reason that there is no written description of clone TR2B packaged in a lambda gt11 phage in the specification. The biological material is

therefore not referenced in the specification and In re Lundak, 773 F.2d 1216, 227 USPQ 90, is not persuasive as applied by Applicant.

4. Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification describes the purification of partial nucleic acids encoding partial amino acid sequences of a single protein species, protein 68075, from a single animal species, human. The specification therefore has a single embodiment that has been shown to work as a transcription factor *in vitro*. It does not adequately describe, give examples, or provide guidance on the purification of nucleic acids from any other animal species or different forms of nucleic acids from the same species that would function as transcription factors because the term "stringent" which is not specifically defined in the disclosure encompasses all degrees of stringency, from low to high stringency and all intermediate stringencies. In other words, the term "stringency" is a relative term open to modification such as "low" stringency" (relatively large number of embodiments) or "high" stringency (relatively lower number of embodiments). In addition, the precise temperature, number of washings, ionic strength, etc. that comprise "stringent" conditions for hybridization (of any degree, low, high, etc.) as compared to non-stringent conditions are not described in sufficient detail or specificity in either the claims or the specification to limit the number of embodiments, so the claims encompass an infinite variety of

nucleic acids that possess little structural similarity to the partial nucleic acid encoding part of protein 68075, and therefore the vast majority of the resultant encoded proteins would not share the functional properties of the amino acid sequence encoded by the deposited clone and therefore the artisan could not use the vast majority of encompassed hybridizing nucleic acids with any reasonable expectation of success. Because the specification only discloses a single embodiment which is not reasonably predictive of either the structure or function of the infinite number of nucleic acids that stringently hybridize to it, undue experimentation would be required to enable hybridizing nucleic acids, if any, that encoded a protein that the skilled artisan could use with a reasonable expectation of success. The instant teachings of the partial nucleic acids does not include any information as to the actual nucleotide sequence of the instant nucleic acids, the nucleotide sequence of nucleic acids from other animal species, or the nucleotide sequence of nucleic acids that hybridize under stringent conditions with the partial nucleic acid that encodes part of protein 68075. Applicant has set forth only functional properties of the claimed genus of hybridizing nucleic acids of instant claim 9 without any structural properties to distinguish that genus. The disclosure does not provide sufficient guidance or examples to enable the chemical genus of claim 9 in the absence of any and all structural limitations.

As taught by the specification (page 5, lines 23-31), it is the encoded protein that possesses the functional property of enhancing the regeneration of a nerve cell process and not the nucleic acid or fragment thereof encoding that protein. Should the grounds of this rejection be overcome, the following scope rejection would be applicable to claims 9-10.

Applicant's arguments filed 11/19/98 have been fully considered but they are not persuasive because Applicant argues that the specification describes six clones. However, all six clones are partial sequences of a single nucleic acid that encodes a single protein with the desired and recited biological properties. The Applicant does not have six embodiments for what is claimed. Applicant asserts that the rejection has been overcome by the amendment but provides no evidence or reasoning and how the rejection is overcome by the amendment is not evident.

5. Claims 9-10 would be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling (if all the grounds of the rejection of ¶4 set forth above are overcome) for a purified nucleic acid comprising Clone ATCC 75949 or a purified fragment of Clone ATCC 75949 that encodes a protein that promotes the regeneration of a process of a central or peripheral neuron *in vitro*, does not reasonably provide enablement for a recombinant nucleic acid that hybridizes with Clone ATCC 97525 or a fragment of Clone ATCC 97525 and enhances [a] neuronal regeneration process. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure does not contain an adequate written description, examples, or guidance to enable language such as "enhances [a] neuronal regeneration process" because this language encompasses *in vivo* use. In order for an encoding nucleic acid to be even remotely considered to possess such a functional property, it would have to be expressed and translated into a protein in

the neuron that required regeneration because it is the protein itself, and not the encoding nucleic acid, that possesses the functional property of neuronal regeneration (see page 5, lines 23-31 of specification). Obstacles to application of nucleic acid drugs *in vivo* are provided by the review of Stull et al. (pages 476-478). Applicant has supplied information on the record asserting that protein 68075 may also be known as transcription factor MEF2C. Transcription factors are proteins that function internally in a cell by binding to DNA in the nucleus. Transcription factors do not work when applied externally to a cell because they do not cross the cell membrane and cannot reach the DNA in the nucleus. Applicant has admitted on the record that he does not claim to have done experiments on human beings (Paper No. 15, filed 1/29/98, page 4). The specification does not contain any working embodiments of animal experiments. The 1.132 declaration of Dr. Krainc indicates that MEF2C gene, also known as clone TR2B, also known as ATCC 75949, also known as a nucleic acid partially encoding protein 68075, when transfected into F19 EC cells *in vitro*, allows the labeling of neurofilaments by antibodies. Dr. Krainc interprets this antibody labeling as being important for neuronal regeneration. However, transfection means that the nucleic acid had to be delivered internally to the cells *in vitro* across the cell membrane, then utilized by the cells to produce the biologically active protein 68075. To accomplish the same results *in vivo* would mean that in order to practice the invention as claimed (enhances neuronal regeneration), gene therapy would have to be successfully performed. The disclosure does not provide a sufficient written description, examples, or guidance for gene therapy to be enabled for the following reasons. Gene therapy has not been performed to date

with a reasonable expectation of success or predictability. For example, the 1995 "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" states that:

"While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in *any gene therapy protocol*, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

Significant problems remain in all basis aspects of gene therapy. Major difficulties at the basic level include *shortcomings in all current gene transfer vectors* and an *inadequate understanding of the biological interaction of these vectors with the host"* [emphasis added; page 1].

Therefore, the lack of working embodiments in the disclosure would force even those of the highest skill in the art to perform undue, not routine, experimentation in order to enable the invention as claimed. Additionally, neurons in the central nervous system do not exist in a supportive environment for their processes to regenerate and active inhibition of such regeneration occurs *in vivo* (see review by Jackowski, pages 305-312).

Applicant's arguments filed 11/19/98 have been fully considered but they are not persuasive because Applicant argues that the specification describes six clones. However, all six clones are partial sequences of a single nucleic acid that encodes a single protein with the desired and recited biological properties. The Applicant does not have six embodiments. Applicant asserts that the rejection has been overcome by the amendment but provides no evidence or reasoning and how the rejection is overcome by the amendment is not evident.

6. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention for reasons of record and the following. Stringent hybridization conditions are not described in the specification to definitively and specifically set forth the metes and bounds of the claim. The specification refers to general guidelines that do not set forth a specific number of washes, a specific temperature, a specific ionic strength of the buffer, etc. that would enable the artisan to determine what is encompassed by the claim. Different recombinant nucleic acids would "stringently" hybridize with Clone ATCC 97525 under different specific conditions of washing, temperature, ionic strength, etc. depending on their nucleotide structure, rendering the claim indefinite.

Applicant's arguments filed 11/19/98 have been fully considered but they are not persuasive because Applicant presents no arguments or amendments directed to this ground of rejection.

7. Claims 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Ullrich et al. ("Ullrich") for reasons of record and the following. Ullrich teaches nucleic acid (Figures 2-3) and fragments (Figure 1) that encode human nerve growth factor (NGF) that possesses the functional property of regenerating neurons, especially sympathetic and sensory neurons (abstract). Since the prior art teaches human nucleic acid that encodes NGF with the functional property recited in the claims, and the specification provides no chemical or structural teachings to distinguish the instant human nucleic acid from the prior art, the prior art is held to be anticipatory, absent evidence to the contrary.

Applicant's arguments filed 11/19/98 have been fully considered but they are not persuasive because Applicant argues that claims referencing deposits are permitted. This argument does not address the prior art rejection under 35 USC 102(b). Applicant also argues that the record purports to show that the material referenced in the specification is a portion of the gene for MEF2 and that the patent system does no credit to maintain an obviousness rejection that is inconsistent with the record. With all due respect, no obviousness rejection has been made of record. The instant claims recite no limitations that would exclude the prior art of record, and Applicant has failed to either amend the claims to provide such limitations or to convincingly argue what limitations currently in the claims exclude the prior art. The specification does not provide support that the instant claims are drawn to a portion of the gene for MEF2, nor are such limitations present in the claims.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Thursday from 0730 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703) 308-3995. The fax phone number for this Group is currently (703) 308-4242, but Applicant should confirm this by phoning the Examiner before faxing.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

February 24, 1999

ANTHONY C. CAPUTA
PRIMARY EXAMINER